

# Osteoporosis Prevention, Diagnosis, and Therapy

## NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy

**O**STEOPOROSIS IS A MAJOR health threat. In the United States alone, 10 million persons already have osteoporosis, and 18 million more have low bone mass, placing them at increased risk for this disorder. Once thought to be a natural part of aging among women, osteoporosis is no longer considered age- or sex-dependent. It is largely preventable due to the remarkable progress in the scientific understanding of its causes, diagnosis, and treatment. Optimization of bone health is a process that must occur throughout life in both men and women. Factors that influence bone health at all ages are essential to prevent osteoporosis and its devastating consequences.

### Consensus Process

The National Institutes of Health organized this 2½-day conference to clarify the factors associated with prevention, diagnosis, and treatment of osteoporosis, and to present the latest information about this disease. After 1½ days of presentations and audience discussion, an independent, nonfederal, 13-member consensus panel chaired by Anne Klibanski, MD, from Harvard Medical School, weighed the scientific evidence and drafted a statement presented to the audience on the third day. Candidates for the panel and speakers were nominated by the planning committee. Panel members' research was in areas adjacent to conference issues and was not used to answer conference questions. The panel represented the fields of internal medicine, family and community medi-

**Objectives** To clarify the factors associated with prevention, diagnosis, and treatment of osteoporosis, and to present the most recent information available in these areas.

**Participants** From March 27-29, 2000, a nonfederal, nonadvocate, 13-member panel was convened, representing the fields of internal medicine, family and community medicine, endocrinology, epidemiology, orthopedic surgery, gerontology, rheumatology, obstetrics and gynecology, preventive medicine, and cell biology. Thirty-two experts from these fields presented data to the panel and an audience of 699. Primary sponsors were the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institutes of Health Office of Medical Applications of Research.

**Evidence** MEDLINE was searched for January 1995 through December 1999, and a bibliography of 2449 references provided to the panel. Experts prepared abstracts for presentations with relevant literature citations. Scientific evidence was given precedence over anecdotal experience.

**Consensus Process** The panel, answering predefined questions, developed conclusions based on evidence presented in open forum and the literature. The panel composed a draft statement, which was read and circulated to the experts and the audience for public discussion. The panel resolved conflicts and released a revised statement at the end of the conference. The draft statement was posted on the Web on March 30, 2000, and updated with the panel's final revisions within a few weeks.

**Conclusions** Though prevalent in white postmenopausal women, osteoporosis occurs in all populations and at all ages and has significant physical, psychosocial, and financial consequences. Risks for osteoporosis (reflected by low bone mineral density [BMD]) and for fracture overlap but are not identical. More attention should be paid to skeletal health in persons with conditions associated with secondary osteoporosis. Clinical risk factors have an important but poorly validated role in determining who should have BMD measurement, in assessing fracture risk, and in determining who should be treated. Adequate calcium and vitamin D intake is crucial to develop optimal peak bone mass and to preserve bone mass throughout life. Supplementation with these 2 nutrients may be necessary in persons not achieving recommended dietary intake. Gonadal steroids are important determinants of peak and lifetime bone mass in men, women, and children. Regular exercise, especially resistance and high-impact activities, contributes to development of high peak bone mass and may reduce risk of falls in older persons. Assessment of bone mass, identification of fracture risk, and determination of who should be treated are the optimal goals when evaluating patients for osteoporosis. Fracture prevention is the primary treatment goal for patients with osteoporosis. Several treatments have been shown to reduce the risk of osteoporotic fractures, including those that enhance bone mass and reduce the risk or consequences of falls. Adults with vertebral, rib, hip, or distal forearm fractures should be evaluated for osteoporosis and given appropriate therapy.

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cine, endocrinology, epidemiology, orthopedic surgery, gerontology, rheumatology, obstetrics and gynecology, preventive medicine, and cell biology. In addition, 32 experts from these same fields presented data to the panel and to a conference audience of 699. Speakers were chosen for research per-

A list of the members of the Consensus Conference Panel appears at the end of this article. A listing of speakers and conference sponsors can be found on the Consensus Development Program Web site at <http://consensus.nih.gov>.

This NIH Consensus Statement, State of the Science Statements, and related materials are available from the NIH Consensus Program Information Center, PO Box 2577, Kensington, MD 20891; (888) 644-2667; or the NIH Consensus Development Program home page at <http://consensus.nih.gov>.

formed in specific areas of concern regarding conference issues.

The literature from the period January 1995 through December 1999 was searched using MEDLINE, and an extensive bibliography of 2449 references was provided to the panel. Experts prepared abstracts for their conference presentations with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.

The panel, answering predefined questions, developed its conclusions based on the scientific evidence presented during the open forum and in the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement. The final consensus statement included supporting references and the conclusions of the consensus panel, and addressed 5 key questions:

1. What is osteoporosis and what are its consequences?
2. How do risks vary among different segments of the population?
3. What factors are involved in building and maintaining skeletal health throughout life?
4. What is the optimal evaluation and treatment of osteoporosis and fractures?
5. What are the directions for future research?

### **1. What Is Osteoporosis and What Are Its Consequences?**

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality. Bone density is expressed as grams of mineral per area or volume, and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation (eg, microfractures), and mineralization. A frac-

ture occurs when a failure-inducing force such as trauma is applied to osteoporotic bone. Thus, osteoporosis is a significant risk factor for fracture, and a distinction between risk factors that affect bone metabolism and risk factors for fracture must be made.

It is important to acknowledge a common misconception that osteoporosis is always the result of bone loss. Bone loss commonly occurs as men and women age; however, an individual who does not reach optimal (ie, peak) bone mass during childhood and adolescence may develop osteoporosis without the occurrence of accelerated bone loss. Hence, suboptimal bone growth in childhood and adolescence is as important as later bone loss in the development of osteoporosis.

Currently there is no accurate measure of overall bone strength. Bone mineral density (BMD) is frequently used as a proxy measure and accounts for approximately 70% of bone strength. The World Health Organization (WHO) operationally defines osteoporosis as bone density 2.5 SDs below the mean for young white adult women. It is not clear how to apply this diagnostic criterion to men and children, or across ethnic groups. Because of the difficulty of accurate measurement and standardization between instruments and sites, controversy exists among experts regarding the continued use of this diagnostic criterion.

Osteoporosis can be further characterized as either primary or secondary. Primary osteoporosis can occur in both sexes at all ages, but often follows menopause in women and occurs later in life in men. In contrast, secondary osteoporosis is a result of medications (eg, glucocorticoids), other conditions (eg, hypogonadism), or diseases (eg, celiac disease).

Osteoporosis has financial, physical, and psychosocial consequences, all of which significantly affect the individual, the family, and the community. An osteoporotic fracture is an outcome of trauma to bone of compromised strength, and its incidence is increased by various other risk factors. Trau-

matic events can range from normal lifting and bending to high-impact falls. The incidence of fracture is high in persons with osteoporosis and increases with age. The probability that a 50-year-old will have a hip fracture during his or her lifetime is 14% for a white woman and 5% to 6% for a white man. The risk for African Americans is much lower (6% and 3% for 50-year-old women and men, respectively).

Osteoporotic fractures, particularly vertebral fractures, can be associated with chronic disabling pain. Nearly one third of patients with hip fractures are discharged to nursing homes within the year following a fracture. Notably, 1 in 5 patients is no longer living 1 year after sustaining an osteoporotic hip fracture. Hip and vertebral fractures are a problem for women in their late 70s and 80s, wrist fractures are a problem for women in their late 50s to early 70s, and all other fractures (eg, pelvis and rib) are a problem throughout the postmenopausal years. Investigators acknowledge the impact of osteoporosis on other systems (eg, gastrointestinal, respiratory, genitourinary, and craniofacial), but reliable prevalence rates are unknown.

Hip fracture has a profound impact on quality of life, as evidenced by findings that 80% of women older than 75 years preferred death to a bad hip fracture resulting in their placement in a nursing home. However, little data exist on the relationship between fractures and psychological and social well-being. Other quality-of-life issues include adverse effects on physical health (eg, skeletal deformity) and on financial resources. An osteoporotic fracture is associated with increased difficulty with the activities of daily life, as only one third of fracture patients regain their prefracture level of function and one third require placement in a nursing home. Fear, anxiety, and depression are frequently reported in women with established osteoporosis, and such consequences are likely under-addressed when considering the overall impact of this condition.

Direct financial expenditures for treatment of osteoporotic fracture in the United States are estimated at \$10 billion to \$15 billion annually. A majority of these estimated costs are due to inpatient care but do not include the costs of treatment for persons without a history of fractures, nor do they include the indirect costs of lost wages or productivity of either the patient or the caregiver. Consequently, these figures significantly underestimate the true costs of osteoporosis. More needs to be learned about these indirect costs, which are considerable.

## 2. How Do Risks Vary Among Different Segments of the Population?

### Sex/Ethnicity

The prevalence of osteoporosis and the incidence of fracture vary by sex and race/ethnicity. White postmenopausal women experience almost three quarters of all hip fractures and have the highest age-adjusted incidence of fracture. Most of the information regarding diagnosis and treatment is derived from research on this population. However, women of other ages, races, and ethnicities, as well as men and children, are also affected. Much of the difference in fracture rates among these groups appears to be explained by differences in peak bone mass and rate of bone loss; however, differences in bone geometry, frequency of falls, and prevalence of other risk factors appear to play a role as well.

Both men and women experience an age-related decline in BMD starting in midlife. Women experience more rapid bone loss in the early years following menopause, which places them at earlier risk for fractures. In men, hypogonadism is also an important risk factor. Men and perimenopausal women with osteoporosis more commonly have secondary causes for the bone loss than do postmenopausal women.

African American women have higher BMD than white non-Hispanic women throughout life, and experience lower rates of hip fracture. For reasons not

fully understood, some Japanese women have lower peak BMDs than white non-Hispanic women, but have lower rates of hip fracture. Mexican-American women have BMDs between those of white non-Hispanic women and African American women. Limited available information for Native American women suggests they have lower BMDs than white non-Hispanic women.

### Risk Factors

Risks associated with low BMD are supported by evidence that includes large prospective studies. Predictors of low bone mass include female sex, increased age, estrogen deficiency, white race, low weight and body mass index (BMI), family history of osteoporosis, smoking, and history of prior fracture. Use of alcohol and caffeine-containing beverages is inconsistently associated with decreased bone mass. In contrast, some measures of physical function and activity have been associated with increased bone mass, including grip strength and current exercise. Levels of exercise in childhood and adolescence have an inconsistent relationship to BMD later in life. Late menarche, early menopause, and low endogenous estrogen levels are also associated with low BMD in several studies.

Although low BMD has been established as an important predictor of future fracture risk, the results of many studies indicate that clinical risk factors related to risk of fall also serve as important predictors of fracture. Fracture risk has been consistently associated with a history of falls, low physical function such as slow gait speed and decreased quadriceps strength, impaired cognition, impaired vision, and the presence of environmental hazards (eg, throw rugs). The risk of a fracture occurring with a fall is increased in tall persons and in falls to the side, and may be influenced by attributes of bone geometry such as hip axis and femur length. Some risks for fracture (eg, advanced age, a low BMI, and low levels of physical activity) probably af-

fect fracture incidence through their effects on bone density, propensity to fall, and inability to absorb impact.

Results of studies of persons with osteoporotic fractures have led to the development of models of risk prediction, which incorporate clinical risk factors along with BMD measurements. Results from the Study of Osteoporotic Fractures, a large longitudinal study of postmenopausal, white, non-Hispanic women, suggest that clinical risk factors can contribute greatly to assessment of fracture risk. In this study, 14 clinical risk factors predictive of fracture were identified. The presence of 5 or more of these factors increased the rate of hip fracture for women in the highest tertile of BMD from 1.1 per 1000 woman-years to 9.9 per 1000 woman-years. Women in the lowest tertile of BMD with no other risk factors had a hip fracture rate of 2.6 per 1000 woman-years, compared with 27.3 per 1000 woman-years among women with 5 or more risk factors. A second model, derived from the Rotterdam study, predicted hip fractures using a smaller number of variables including sex, age, height, weight, use of a walking aid, and current smoking. However, these models have not been validated in a population different from that in which they were derived.

### Secondary Osteoporosis

A large number of medical disorders are associated with osteoporosis and increased risk of fracture. These can be organized into several categories: genetic disorders, hypogonadal states, endocrine disorders, gastrointestinal diseases, hematologic disorders, connective tissue diseases, nutritional deficiencies, drugs, and a variety of other common serious chronic systemic disorders such as congestive heart failure, end-stage renal disease, and alcoholism.

The distribution of the most common causes appears to differ by demographic group. Among men, 30% to 60% of osteoporosis cases are associated with secondary causes, the most common of which are hypogonadism,

use of glucocorticoids, and alcoholism. In perimenopausal women, more than 50% of cases are associated with secondary causes, the most common of which are hypoestrogenemia, use of glucocorticoids, thyroid hormone excess, and anticonvulsant therapy. In postmenopausal women, the prevalence of secondary conditions is thought to be much lower, but the actual proportion is not known. In 1 study, hypercalciuria, hyperparathyroidism, and malabsorption were identified in a group of white postmenopausal women with osteoporosis who had no history of conditions that cause bone loss. These data suggest that additional testing of such women may be indicated, but an appropriate or cost-effective evaluation strategy has not been determined.

Glucocorticoid use causes the most common form of drug-related osteoporosis, and the long-term administration of glucocorticoids for disorders such as rheumatoid arthritis and chronic obstructive pulmonary disease is associated with a high rate of fracture. For example, in 1 study, a group of patients treated with 10 mg/d of prednisone for 20 weeks experienced an 8% loss of BMD in the spine. Some experts suggest that any patient who receives prednisone or other orally administered glucocorticoids in a dose of 5 mg/d or more for longer than 2 months is at high risk for excessive bone loss.

People who have undergone organ transplantation are at high risk for osteoporosis due to a variety of factors, including pretransplant organ failure and use of glucocorticoids after transplantation.

Hyperthyroidism is a well-described risk factor for osteoporosis. In addition, some studies have suggested that women receiving thyroid replacement therapy may also be at increased risk for excessive bone loss, suggesting that careful regulation of thyroid replacement is important.

### Children and Adolescents

Several groups of children and adolescents may be at risk for compromised

bone health. Premature and low-birth-weight infants have lower-than-expected bone mass in the first few months of life, but the long-term implications of this are unknown.

Glucocorticoids are now commonly used for the treatment of a variety of common childhood inflammatory diseases, and the effects of this treatment on bone need to be considered when chronic use of steroids is required. The long-term effects on bone health of intermittent courses of systemic steroids or the chronic use of inhaled steroids, such as those used in asthma, are not well described.

Cystic fibrosis, celiac disease, and inflammatory bowel disease are examples of conditions associated with malabsorption and resultant osteopenia in some persons. The osteoporosis of cystic fibrosis is also related to the frequent need for corticosteroids as well as to other undefined factors.

Hypogonadal states, characterized clinically by delayed menarche, oligomenorrhea, or amenorrhea, are relatively common in adolescent girls and young women. These occur with strenuous athletic training, emotional stress, and low body weight. Failure to achieve peak bone mass, bone loss, and increased fracture rates have been shown in this group. Anorexia nervosa deserves special mention. Although hypogonadism is an important feature of the clinical picture, undernutrition and other nutrition-related factors are also critical. This latter point is evidenced, in part, by the failure of estrogen replacement to correct the bone loss.

### Residents of Long-term Care Facilities

Residents of nursing homes and other long-term care facilities are at particularly high risk of fracture. Most have low BMD and a high prevalence of other risk factors for fracture, including advanced age, poor physical function, low muscle strength, poor nutrition, decreased cognition and high rates of dementia, and, often, use of multiple medications.

### 3. What Factors Are Involved in Building and Maintaining Skeletal Health Throughout Life?

Growth in bone size and strength occurs during childhood, but bone accumulation is not completed until the third decade of life, after the cessation of linear growth. The bone mass attained early in life is perhaps the most important determinant of lifelong skeletal health. Persons with the highest peak bone mass after adolescence have the greatest protective advantage when bone density declines as a result of aging, illness, and diminished sex-steroid production. Bone mass may be related not only to osteoporosis and fragility later in life but also to fractures in childhood and adolescence. Genetic factors exert a strong and perhaps predominant influence on peak bone mass, but physiological, environmental, and modifiable lifestyle factors can also play a significant role. Among these are adequate nutrition and body weight, exposure to sex hormones at puberty, and physical activity. Thus, maximizing bone mass early in life presents a critical opportunity to reduce the impact of bone loss related to aging. Childhood is also a critical time for the development of lifestyle habits conducive to maintaining good bone health throughout life. Cigarette smoking, which usually starts in adolescence, may have a deleterious effect on achieving bone mass.

### Nutrition

Good nutrition is essential for normal growth. A balanced diet, adequate calories, and appropriate nutrients are the foundation for development of all tissues, including bone. Supplementation with calcium and vitamin D may be necessary. Adequate and appropriate nutrition is important for all persons, but not all follow a diet that is optimal for bone health. In particular, excessive pursuit of thinness may preclude adequate nutrition and affect the health of bone.

Calcium is the nutrient most important for attaining peak bone mass and for preventing and treating osteoporosis.

sis. Sufficient data exist to recommend specific dietary calcium intakes at various stages of life. Although the Institute of Medicine recommends calcium intakes of 800 mg/d for children aged 3 to 8 years and 1300 mg/d for children and adolescents aged 9 to 17 years, it is estimated that only about 25% of boys and 10% of girls aged 9 to 17 years meet these recommendations. Factors contributing to low calcium intakes are restriction of dairy products, a generally low consumption of fruits and vegetables, and a high intake of low-calcium beverages such as sodas. For older adults, calcium intake should be maintained at 1000 to 1500 mg/d, yet only about 50% to 60% of this population meets this recommendation.

Vitamin D is required for optimal calcium absorption and thus is also important for bone health. Most infants and young children in the United States have adequate vitamin D intake because of supplementation and fortification of milk. During adolescence, when consumption of dairy products decreases, vitamin D intake is less likely to be adequate, and this may adversely affect calcium absorption. A recommended vitamin D intake of 400 to 600 IU/d has been established for adults.

Other nutrients have been evaluated for their relation to bone health. High dietary protein, caffeine, phosphorus, and sodium can adversely affect calcium balance, but their effects appear not to be important in individuals with adequate calcium intakes.

### Exercise

Regular physical activity has numerous health benefits for persons of all ages. The specific effects of physical activity on bone health have been investigated in randomized clinical trials (RCTs) and observational studies. There is strong evidence that physical activity early in life contributes to higher peak bone mass. Some evidence indicates that resistance and high-impact exercise are likely the most beneficial. Exercise during the middle years of life has numerous health benefits, but there

are few studies of the effects of exercise on BMD. Exercise during the later years, in the presence of adequate calcium and vitamin D intake, probably has a modest effect on slowing the decline in BMD. It is clear that exercise late in life, even beyond age 90 years, can increase muscle mass and strength 2-fold or more in frail persons. There is convincing evidence that exercise in elderly persons also improves function and delays loss of independence and thus contributes to quality of life.

Randomized clinical trials of exercise have been shown to reduce the risk of falls by approximately 25%, but there is no experimental evidence that exercise affects fracture rates. It also is possible that regular exercisers might fall differently and thereby reduce the risk of fracture due to falls, but this hypothesis requires testing.

### Gonadal Steroids

Sex steroids secreted during puberty substantially increase BMD and peak bone mass. Gonadal steroids influence skeletal health throughout life in both women and men. In adolescents and young women, sustained production of estrogens is essential for the maintenance of bone mass. Reduction in estrogen production at menopause is the major cause of loss of BMD during later life. Timing of menarche, absent or infrequent menstrual cycles, and the timing of menopause influence both the attainment of peak bone mass and the preservation of BMD. Testosterone production in adolescent boys and men is similarly important in achieving and maintaining maximal bone mass. Estrogens have also been implicated in the growth and maturation of the male skeleton. Pathologic delay in the onset of puberty is a risk factor for diminished bone mass in men. Disorders involving hypogonadism in adult men result in osteoporosis.

### Growth Hormone and Body Composition

Growth hormone and insulin-like growth factor I, which are maximally secreted during puberty, continue to play

a role in the acquisition and maintenance of bone mass and the determination of body composition into adulthood. Growth hormone deficiency is associated with a decrease in BMD. Children and youth with low BMI are likely to attain lower-than-average peak bone mass. Although there is a direct association between BMI and bone mass throughout the adult years, it is not known whether the association between body composition and bone mass is due to hormones, nutrition, higher impact during weight-bearing activities, or other factors. There are several observational studies of fractures in older persons that show an inverse relationship between fracture rates and BMI.

### 4. What Is the Optimal Evaluation and Treatment of Osteoporosis and Fractures?

The goals for the evaluation of patients at risk for osteoporosis are to establish the diagnosis of osteoporosis on the basis of assessment of bone mass, to establish the fracture risk, and to make decisions regarding the needs for instituting therapy. A history taking and physical examination are essential in evaluating fracture risks and should include assessment for loss of height and change in posture. Laboratory evaluation for secondary causes of osteoporosis should be considered when osteoporosis is diagnosed.

The measurement most commonly used to diagnose osteoporosis and predict fracture risk is based on assessment of BMD. Measurements of BMD have been shown to correlate strongly with load-bearing capacity of the hip and spine and with the risk of fracture. Several different techniques have been developed to assess BMD at multiple skeletal sites including the peripheral skeleton, hip, and spine. The WHO has selected BMD measurements to establish criteria for the diagnosis of osteoporosis. A T score is defined as the number of SDs above or below the average BMD value for young healthy white women. This should be distinguished from a Z score, which is defined as the number of SDs above or below the average BMD for age-



and sex-matched controls. According to the WHO definition, osteoporosis is present when the T score is at least  $-2.5$  SDs. Although T scores were based originally on assessment of BMD at the hip by dual-energy x-ray absorptiometry (DXA), they have been applied to define diagnostic thresholds at other skeletal sites and for other technologies. Experts have expressed concern that this approach may not produce comparable data between sites and techniques. Of the various sampling sites, measurements of BMD made at the hip predict hip fracture better than measurements made at other sites while BMD measurement at the spine predicts spine fracture better than measures at other sites.

Newer measures of bone strength, such as ultrasound, have been introduced. Recent prospective studies using quantitative ultrasound (QUS) of the heel have predicted hip fracture and all nonvertebral fractures nearly as well as DXA at the femoral neck. Quantitative ultrasound and DXA at the femoral neck provide independent information about fracture risk, and both of these tests predict hip fracture risk better than DXA at the lumbar spine. In general, clinical trials of pharmacological therapies have used DXA, rather than QUS, for entry criterion for studies, and there is uncertainty regarding whether the results of these trials can be generalized to patients identified by QUS to have a high risk of fracture.

Over the past year, several professional organizations have been working on establishing a standard of comparability of different devices and sites for assessing fracture risk. With this approach, measurements derived from any device or site could be standardized to predict hip fracture risk. However, the values obtained from different instruments cannot be used to predict comparable levels in bone mass. Limitations in precision and low correlation among different techniques will require appropriate validation before this approach can be applied to different skeletal sites and to different age groups.

It has been suggested that the diagnosis and treatment of osteoporosis

should depend on risk-based assessment rather than solely on the assessment of a T score. Consideration of risk factors in conjunction with BMD will likely improve the ability to predict fracture risk. This approach needs to be validated in prospective studies and tested in appropriate RCTs.

In addition to the effects of bone mass, microarchitecture, and macrogeometry, bone strength is also affected by the rate of remodeling. Bone remodeling can be assessed by the measurement of surrogate markers of bone turnover in the blood or urine. These markers include indices of bone formation, such as bone-specific alkaline phosphatase and osteocalcin, and urine levels of pyridinolines and deoxypyridinolines, as well as indices of bone resorption such as serum and urine levels of type I collagen C- and N-telopeptides. The levels of these markers may identify changes in bone remodeling within a relatively short interval (several days to months) before changes in BMD can be detected. However, according to available data, marker levels do not predict bone mass or fracture risk and are only weakly associated with changes in bone mass. Therefore, they are of limited use in the clinical evaluation of individual patients. Despite these limitations, markers have been shown in research studies to correlate with changes in indices of bone remodeling and may provide insights into mechanisms of bone loss.

#### Who Should Be Evaluated?

The value of bone density in predicting fracture risk is established, and there is general consensus that measurement of BMD should be considered in patients receiving glucocorticoid therapy for 2 months or more and in patients with other conditions that place them at high risk for osteoporotic fracture. However, the value of universal screening, especially in perimenopausal women, has not been established. There are 2 unknown factors with this approach.

First, the number of women evaluated and treated would need to be high

to prevent a single fracture. For example, in white women aged 50 to 59 years, an estimated 750 BMD tests would be required to prevent just 1 hip or vertebral fracture over a 5-year period of treatment. Second, the value has not been established for the common practice of beginning preventive drug therapy in the perimenopausal period for the purpose of preventing fractures later in life.

Until there is good evidence to support the cost-effectiveness of routine screening, or the efficacy of early initiation of preventive drugs, an individualized approach is recommended. A measurement of BMD should be considered when it will help the patient decide whether to institute treatment to prevent osteoporotic fracture. In the future, a combination of risk factor evaluation and BMD measurements may increase the ability to predict fracture risk and help with treatment decisions. Until RCTs are conducted, individual decisions regarding screening could be informed by the preliminary evidence that the risk for fracture increases with age, and with an increased number of additional risk factors.

#### What Are the Effective Medical Treatments?

In the past 30 years, major strides have been made in the treatment of osteoporosis. Evidence-based reports systematically reviewing the data from RCTs, including meta-analyses for each of the major treatments, are available and permit conclusions regarding the role of each modality of osteoporosis therapy.

Calcium and vitamin D intake modulates age-related increases in parathyroid hormone (PTH) levels and bone resorption. Randomized clinical trials have demonstrated that adequate calcium intake from diet or supplements increases spinal BMD and reduces vertebral and nonvertebral fractures. Low levels of 25-hydroxyvitamin D are common in the aging population, and significant reductions in hip and other nonvertebral fractures have been observed in patients receiving calcium and

vitamin D<sub>3</sub> in prospective trials. The optimal effective dose of vitamin D is uncertain, but thought to be 400 to 1000 IU/d. There is consensus that adequate vitamin D and calcium intakes are required for bone health. The therapeutic effects of most of the clinical trials of various drug therapies for osteoporosis have been achieved in the presence of calcium and vitamin D supplementation among control and intervention groups. Optimal treatment of osteoporosis with any drug therapy also requires calcium and vitamin D intake meeting recommended levels. The preferred source of calcium is dietary. Calcium supplements need to be absorbable and should have United States Pharmacopeia designation.

Physical activity is necessary for bone acquisition and maintenance through adulthood. Complete bed rest and microgravity have devastating effects on bone. Trials of exercise intervention show most of the effect during skeletal growth and in very inactive adults. Effects beyond those directly on bone, such as improved muscular strength and balance, may be very significant in the reduction of fracture risk. Trials in older adults have successfully used various forms of exercise to reduce falls. High-impact exercise such as weight training stimulates accrual of bone mineral content in the skeleton. Lower-impact exercises, such as walking, have beneficial effects on other aspects of health and function, although their effects on BMD have proved minimal.

Placebo-controlled RCTs of cyclic etidronate, alendronate, and risedronate analyzed by a systematic review and meta-analysis have revealed that all of these bisphosphonates increase BMD at the spine and hip in a dose-dependent manner. They consistently reduce the risk of vertebral fractures by 30% to 50%. Alendronate and risedronate reduce the risk of subsequent nonvertebral fractures in women with osteoporosis and adults with glucocorticoid-induced osteoporosis. There is uncertainty about the effect of antiresorptive therapy in reducing nonvertebral fracture in women without osteoporosis. In RCTs, the rela-

tive risk of discontinuing medication due to an adverse event with each of the 3 bisphosphonates was not statistically significant. The safety and efficacy of this therapy in children and young adults has not been evaluated. Since subjects in clinical trials may not always be representative of the community-based population, an individual approach to treatment is warranted.

Hormone replacement therapy (HRT) is an established approach for osteoporosis treatment and prevention. Many short-term studies and some longer-term studies of HRT with BMD as the primary outcome have shown significant efficacy. Observational studies have indicated a significant reduction in the occurrence of hip fracture in cohorts of women who maintain HRT therapy; still, there is a paucity of trials with fractures as the end point. Trials of HRT have shown decreased risk of vertebral fractures, but there have been no trials of estrogen having hip fracture as the primary outcome.

The development of selective estrogen-receptor modulators (SERMs) has been an important new thrust in osteoporosis research. The goal of these agents is to maximize the beneficial effect of estrogen on bone and to minimize or antagonize the deleterious effects on the breast and endometrium. Raloxifene, a SERM approved by the Food and Drug Administration for the treatment and prevention of osteoporosis, has been shown to reduce the risks of vertebral fracture by 36% in large clinical trials. Tamoxifen, used in the treatment and prevention of breast cancer, can maintain bone mass in postmenopausal women. However, tamoxifen's effects on the risk of fracture are unclear.

There is a great deal of public interest in natural estrogens, particularly plant-derived phytoestrogens. These compounds have weak estrogen-like effects, and although some animal studies are promising, no reduction in risk of fracture in humans has been shown. Salmon calcitonin has demonstrated positive effects on BMD at the lumbar spine, but this effect is less clear at the hip. Other than a recently completed

RCT of nasal calcitonin, no analysis of fracture risk is available. The Prevent Recurrence of Osteoporotic Fractures (PROOF) study revealed a significant reduction in vertebral fracture risk at the 200 IU daily dose but not at the 100 IU or 400 IU daily doses. The absence of dose response, a 60% dropout rate, and the lack of strong supporting data from BMD and markers decrease confidence in the fracture risk data from this trial. Nonpharmacological interventions directed at preventing falls and reducing their effect on fractures have been promising. These include improving strength and balance in the elderly, as well as using hip protectors to absorb or deflect the impact of a fall.

Multifactorial approaches to preventing falls, as well as improving bone mass through combinations of interventions, suggest promising new directions.

#### **Should the Response to Treatment Be Monitored?**

Several approaches have been introduced for the monitoring of patients receiving therapies for osteoporosis. The goals of monitoring are to increase adherence to treatment regimens and determine treatment responses. Many persons do not continue prescribed therapy or do not adhere to a treatment protocol, even when enrolled in formal clinical trials. Monitoring by densitometry or measurements of bone markers have not been effective in improving compliance, and more research is needed to determine how to improve adherence to treatment protocols.

The best tests for monitoring treatment response would reflect the largest changes with the least error, and these assessment tools are not readily available. The Fracture Intervention Trial (FIT) reveals an additional problem with monitoring, namely, the statistical phenomenon of regression to the mean. In the FIT study, the larger the bone loss in the first year the greater the gain the next year, for both the placebo and active treatment groups. Therefore, physicians should not stop or change therapies with demonstrated efficacy solely

because of modest loss of bone density or adverse trends in markers of bone turnover.

### Orthopedic Management of Osteoporotic Fractures

Proximal femur (hip) fractures comprise nearly 20% of all osteoporotic fractures. This injury is among the most devastating of all the osteoporotic fractures and is responsible for the greatest expenditure of health care resources. The 1-year mortality rate following hip fracture is about 1 in 5. As many as two thirds of hip fracture patients never regain their preoperative activity status. Early surgical management of hip fractures is associated with improved outcomes and decreased perioperative morbidity.

The adverse effects of vertebral fractures on health, function, and quality of life are commonly underestimated; such fractures are also associated with increased mortality. The occurrence of a single vertebral fracture substantially increases the likelihood of future fractures and progressive kyphotic deformity. Due to the challenges of reconstructing osteoporotic bone, open surgical management is reserved only for those rare cases involving neurologic deficits or an unstable spine. Recently, there has been a burgeoning interest in 2 minimally invasive procedures for management of acute vertebral fractures. These procedures, vertebroplasty and kyphoplasty, involve the injection of polymethylmethacrylate bone cement into the fractured vertebra. Anecdotal reports of both techniques frequently claim relief of acute pain; however, neither technique has been subjected to a controlled trial to demonstrate the benefits over traditional medical management. Furthermore, the long-term effect of 1 or more reinforced rigid vertebrae on the risk of fracture of adjacent vertebrae is unknown for both of these procedures.

Several issues are critically important to the management of acute osteoporotic fractures. It is most important to avoid the misconception that the only treatment required for an osteoporotic

fracture is management of the acute fracture itself. Management during the perifracture period must consider blood clot prevention (mechanical or pharmacological) in patients who will have delayed ambulation, the avoidance of substances that may inhibit fracture repair (eg, nicotine, corticosteroids), and the frequent need for supplemental caloric intake. Finally, since less than 5% of patients with osteoporotic fractures are referred for medical evaluation and treatment, more aggressive diagnostic and therapeutic intervention of this population represents an opportunity to prevent subsequent fractures. Physicians treating the acute fracture should initiate an outpatient evaluation of the patient for osteoporosis and a treatment program, if indicated, or refer the patient for an osteoporosis assessment.

### 5. What Are the Directions for Future Research?

The following questions, issues, and concerns should be addressed:

- Peak bone mass is an important factor in determining long-term fracture risk. Strategies to maximize peak bone mass in girls and boys are essential. These strategies include identifying and intervening in disorders that can impede the achievement of peak bone mass in ethnically diverse populations, and determining how long these interventions should last. More research regarding the risks for fracture in chronic diseases affecting children is needed. What is the impact of calcium deficiency and vitamin D deficiency in childhood, and can it be reversed? How does gonadal steroid insufficiency, pubertal delay, or undernourishment impact bone mass? What is known about the use of bisphosphonates or other agents in the treatment of children with osteoporosis?

- Genetic factors leading to osteoporosis are being identified. These factors may relate to bone mass acquisition, bone remodeling, or bone structure. Pharmacogenetic approaches for identifying and targeting specific genetic factors predisposing to osteoporosis need to be developed.

- Glucocorticoid use is a common cause of secondary osteoporosis and associated fractures. What is the impact of glucocorticoid-induced osteoporosis in adults and children? What are the mechanisms of disease? What novel approaches can be taken to stimulate bone formation in this condition? Development of glucocorticoids having fewer adverse effects on the skeleton are needed.

- Secondary causes of osteoporosis are prevalent. A number of risk factors have been identified, including specific disease states and medication use. How should patients be identified for diagnosis and treatment of osteoporosis? What is known about the use of bisphosphonates or other agents in young adults with secondary osteoporosis? What is known about the causes of osteoporosis in perimenopausal women? How should they be monitored for treatment response? Are therapies for improving bone mass in postmenopausal women effective in secondary causes?

- There is a need for prospective studies of sex, age, and ethnic diversity to provide data permitting more accurate fracture risk identification in these categories. Fracture risk is a combination of bone-dependent and bone-independent factors. Bone-independent factors include muscle function and cognition, which also contribute to falls leading to fractures. A comprehensive assessment of bone-dependent and bone-independent factors should be included. There is a need for a comprehensive evaluation of a validated risk assessment tool. What is the best way to identify patients in need of treatment for osteoporosis? An algorithm should be constructed that incorporates risk factors for fracture in addition to assessment of bone density. What is the best use of surrogate markers of bone turnover to determine osteoporosis, and how does this impact on fracture risks?

- Quality of life is significantly impaired by osteoporosis. Future research should characterize and validate quality-of-life tools in patients across sex, age, and race/ethnicity categories.



egories. It will be important to identify effects of fracture risk and intervention on quality of life. Quality of life should be incorporated as an outcome in clinical trials evaluating fracture risk and therapy. In addition, the psychosocial and financial effects of osteoporosis on caregivers and on family dynamics should be considered.

- Data should be obtained suggesting which asymptomatic patients should have screening bone-density tests done or when screening is justified.

- Neuropsychiatric disorders may cause or be the result of osteoporosis. Specific psychiatric disorders, including depression and anorexia nervosa, are associated with osteoporosis or clinical fractures. Medications used to treat psychiatric or neurologic disorders may cause osteoporosis, and the diagnosis of osteoporosis may have psychological implications. Research efforts into these relationships should be strongly encouraged.

- There is an urgent need for RCTs of combination therapy, which includes pharmacological, dietary, and lifestyle interventions (including muscle strengthening, balance training, management of multiple drug use, smoking cessation, psychological counseling, and dietary interventions). Primary outcomes would be fractures, and secondary outcomes would include quality of life and functional capability. Cost-effectiveness evaluations should also be considered.

- What is the optimal paradigm for the evaluation and management of fractures? What are the long-term consequences of osteoporosis and clinical fractures on nonskeletal body systems? What measures can be taken to prevent subsequent fractures?

- Anabolic agents that stimulate bone formation, such as PTH and fluoride, have been evaluated. Meta-analysis of fluoride therapy revealed no protective effects on fracture risk. Parathyroid hormone peptides are the most promising but are still in clinical trials. Other factors, including growth hormones, are under investigation. There is a critical need to develop and assess

anabolic agents that stimulate bone formation.

- Ensure accessibility to treatment regardless of income and geography.

- There is a need to determine the most effective method of educating health care professionals and the public about the prevention, diagnosis, and treatment of osteoporosis.

- There is a need to improve the reporting of BMD and fracture risk so it is understandable to medical specialists and can be explained to patients.

- Study is needed to determine the efficacy and safety of long-term administration of various drug interventions in maintaining BMD and preventing fractures.

- Trials of dietary supplements are needed.

- Study is needed to understand the influence of nutrition on micronutrients and nonpatentable medical interventions.

- Study is needed to understand cost-effectiveness and effectiveness of programs encouraging bone health.

- Study of interventions examining the long-term effects of fractures on health, function, and quality of life is needed.

**NIH Consensus Development and State of the Science Conferences** are convened to evaluate available scientific information and resolve safety and efficacy issues related to biomedical technology. The resultant statements are intended to advance understanding of the technology or issue in question and to be useful to health professionals and the public. **This statement is an independent report of the panel and is not a policy statement of the NIH or the federal government.**

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Division of Pediatric Endocrinology, Vanderbilt University Medical Center, Nashville, Tenn. The abstract is prepared by the conference organizers and added to the consensus conference panel's statement as a service for JAMA readers.

# Bibliography

The consensus conference speakers identified the following key references in developing their presentations for the consensus conference. A more complete bibliography prepared by the National Library of Medicine, along with the references below, was provided to the technology assessment panel for their consideration. The full bibliography is available at: <http://www.nlm.nih.gov/pubs/cbm/osteoporosis.html>.

## What Is Osteoporosis and What Are Its Consequences?

Bravo G, Gauthier P, Roy PM, et al. Impact of a 12-month exercise program on the physical and psychological health of osteopenic women. *J Am Geriatr Soc*. 1996;44:756-762.

Burr D, Forwood M, Fyhr D, et al. Bone microdamage and skeletal fragility in osteoporotic and stress fractures. *J Bone Miner Res*. 1997;12:6-15.

Carter DR, Hayes WC. The compressive behavior of bone as a two-phase porous structure. *J Bone Joint Surg Am*. 1977;59:954-962.

Chrischilles E, Shireman T, Wallace R. Costs and health effects of osteoporotic fractures. *Bone*. 1994;15:377-387.

Compston J. Connectivity of cancellous bone. *Bone*. 1994;15:463-466.

Cranney A, Welch V, Lee K, Tugwell P. A review of economic evaluation in osteoporosis. *Arthritis Care Res*. 1999;12:425-434.

Cummings SR, Browner WS, Bauer D, et al, for the Study of Osteoporotic Fractures Research Group. Endogenous hormones and the risk of hip and vertebral fractures among older women. *N Engl J Med*. 1998;339:733-738.

Ettinger B, Block JE, Smith R, et al. An examination of the association between vertebral deformities, physical disabilities and psychosocial problems. *Maturitas*. 1988;10:283-296.

Ferrucci L, Guralnik J, Pahor M, Corti M, Havlik R. Hospital diagnoses, Medicare charges, and nursing home admissions in the year when older persons become severely disabled. *JAMA*. 1997;277:728-734.

Genant HK, Gordon C, Jiang Y, et al. Advanced imaging of bone macro and micro structure. *Bone*. 1999;25:149-152.

Gold DT. The clinical impact of vertebral fractures. *Bone*. 1996;18:185S-190S.

Gold DT, Stegmaier K, Bales CW, et al. Psychosocial functioning and osteoporosis in late life. *J Womens Health*. 1996;2:149-155.

Gold M, Siegel J, Russell L, Weinstein M, eds. *Cost-effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.

Goldstein S, Goulet R, McCubrey D. Measurement and significance of three-dimensional architecture to the mechanical integrity of trabecular bone. *Calcif Tissue Int*. 1993;53(suppl 1):S127-S133.

Hodgson T, Meiners M. Cost-of-illness methodology. *Milbank Mem Fund Q*. 1982;60:429-462.

Hoerger TJ, Downs KE, Lakshmanan MC, et al. Health-care use among U.S. women aged 45 and older. *J Womens Health Gend Based Med*. 1999;8:1077-1089.

Holbrook T, Grazier K, Kelsey J, Sauffer R. *The Frequency of Occurrence, Impact, and Cost of Musculoskeletal Conditions in the United States*. Park Ridge, Ill: American Academy of Orthopaedic Surgeons; 1984.

Jonsson B, Kanis J, Dawson A, et al. Effect and offset of effect of treatments for hip fracture on health outcomes. *Osteoporos Int*. 1999;10:193-199.

Kanis JA, Melton LJ III, Christiansen C, et al. Perspective: the diagnosis of osteoporosis. *J Bone Miner Res*. 1994;9:1137-1141.

- Khosla S, Melton LJ III, Atkinson EJ, et al. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women. *J Clin Endocrinol Metab*. 1998;83:2266-2274.
- Lauritzen JB, Petersen MM, Lund B. Effect of external hip protectors on hip fractures. *Lancet*. 1993;341:11-13.
- Leidig-Bruckner G, Minne HW, Schlaich C, et al. Clinical grading of spinal osteoporosis. *J Bone Miner Res*. 1997;12:663-675.
- Looker AC, Orwoll ES, Johnston CC Jr, et al. Prevalence of low femoral bone density in older U.S. adults from NHANES III. *J Bone Miner Res*. 1997;12:1761-1768.
- Malmros B, Mortensen L, Jensen MB, Charles P. Positive effects of physiotherapy on chronic pain and performance in osteoporosis. *Osteoporos Int*. 1998;8:215-221.
- Marcus R, Greendale G, Blunt BA, et al. Correlates of bone mineral density in the Postmenopausal Estrogen/Progestin Interventions Trial. *J Bone Miner Res*. 1994;9:1467-1476.
- Melton LJ III, Atkinson EJ, O'Connor MK, et al. Bone density and fracture risk in men. *J Bone Miner Res*. 1998;13:1915-1923.
- Mori S, Harruf R, Ambrosius W, Burr D. Trabecular bone volume and microdamage accumulation in the femoral heads of women with and without femoral neck fractures. *Bone*. 1997;21:521-526.
- Myers E, Wilson S. Biomechanics of osteoporosis and vertebral fractures. *Spine*. 1997;22:255-315.
- Norman T, Wang Z. Microdamage of human cortical bone. *Bone*. 1997;20:375-379.
- Phillips S, Fox N, Jacobs J, Wright W. The direct medical cost of osteoporosis for American women aged 45 and older. *Bone*. 1988;9:271-279.
- Pocock NA, Eisman JA, Hopper JL, et al. Genetic determinants of bone mass in adults. *J Clin Invest*. 1987;80:706-710.
- Praemer A, Furner S, Rice D, eds. *Musculoskeletal Conditions in the United States*. Park Ridge, Ill: American Academy of Orthopaedic Surgeons; 1992.
- Praemer A, Furner S, Rice D. *Musculoskeletal Conditions in the United States*. 2nd ed. Rosemont, Ill: American Academy of Orthopaedic Surgeons; 1999.
- Randell A, Sambrook P, Nguyen T, et al. Direct clinical and welfare costs of osteoporotic fractures in elderly men and women. *Osteoporos Int*. 1995;5:427-432.
- Ray N, Chan J, Thamer M, Melton LJ III. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995. *J Bone Miner Res*. 1997;12:24-35.
- Rice JC, Cowin SC, Bowman JA. On the dependence of the elasticity and strength of cancellous bone on apparent density. *J Biomech*. 1988;21:155-168.
- Riggs BL, Khosla S, Melton LJ III. A unitary model for involutional osteoporosis. *J Bone Miner Res*. 1998;13:763-773.
- Roberto KA. Adjusting to chronic disease: the osteoporotic woman. *J Women Aging*. 1990;2:33-47.
- Roberto KA. Stress and adaptation patterns of older osteoporotic women. *Women Health*. 1988;14:105-119.
- Ross PD, Ettinger B, Davis JW, et al. Evaluation of adverse health outcomes associated with vertebral fractures. *Osteoporos Int*. 1991;1:134-140.
- Seeman E. From density to structure: growing up and growing old on the surfaces of bone. *J Bone Miner Res*. 1997;12:509-521.
- Seeman E. Growth in bone mass and size: are racial and gender differences in bone mineral density more apparent than real? *J Clin Endocrinol Metab*. 1998;83:1414-1418.
- Tosteson A, Rosenthal D, Melton LJ III, Weinstein M. Cost-effectiveness of screening premenopausal white women for osteoporosis. *Ann Intern Med*. 1990;113:594-603.
- US Bureau of the Census. *Population Projections of the United States by Age, Sex, Race and Hispanic Origin, 1995 to 2050*. Washington, DC: US Bureau of the Census; 1996. Report P25-1130.
- Varney LF, Parker RA, Vincelette A, Greenspan SL. Classification of osteoporosis and osteopenia in postmenopausal women is dependent on site-specific analysis. *J Clin Densitom*. 1999;2:275-283.
- How Do Risks Vary Among Different Segments of the Population?**
- Buckley LM, Leib ES, Cartularo KS, et al. Calcium and vitamin D3 supplementation prevents bone loss in the spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis. *Ann Intern Med*. 1996;125:961-968.
- Cheng S, Suominen H, Sakari-Rantala R, et al. Calcaneal bone mineral density predicts fracture occurrence. *J Bone Miner Res*. 1997;12:1075-1082.
- Chu CQ, Allard S, Abney E, et al. Detection of cytokines at the cartilage/pannus junction in patients with rheumatoid arthritis. *Br J Rheumatol*. 1992;32:653-661.
- Ebbesen EB, Thomsen JS, Beck-Nielsen H, et al. Lumbar vertebral body compressive strength evaluated by dual-energy x-ray absorptiometry, quantitative computed tomography, and ashing. *Bone*. 1999;6:713-724.
- Kong YY, Feige U, Sarosi I, et al. Activated T cells regulate bone loss and joint destruction in adjunct arthritis through osteoprotegerin ligand. *Nature*. 1999;402:304-309.
- Kotake S, Udagawa N, Takahashi N, et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J Clin Invest*. 1999;103:1345-1352.
- Lane NE, Sanchez S, Modin GW, et al. Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. *J Clin Invest*. 1998;102:1627-1633.
- Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis. *Ann Intern Med*. 1990;112:352-364.
- Lunt M, Felsenberg D, Reeve J, et al. Bone density variation and its effects on risk of vertebral deformity in men and women studied in thirteen European centers: the EVOS Study. *J Bone Miner Res*. 1997;12:1883-1894.
- Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ*. 1996;333:1254-1259.
- Nguyen T, Sambrook P, Kelly P, et al. Prediction of osteoporotic fractures by postural instability and bone density. *BMJ*. 1993;307:1111-1115.
- Rodino M, Shane E. Osteoporosis after organ transplantation. *Am J Med*. 1998;104:459-469.
- Ross PD, Lombardi A, Freedholm D. The assessment of bone mass in men. In: Orwoll ES, ed. *Osteoporosis in Men: The Effects of Gender on Skeletal Health*. San Diego, Calif: Academic Press; 1999:505-525.
- Saag KG, Emkey R, Schnitzer A, et al, for the Glucocorticoid-Induced Osteoporosis Intervention Study Group. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *N Engl J Med*. 1998;339:292-299.
- Shane E. Osteoporosis secondary to illness and medications. In: Marcus R, Feldman D, Kelsey J, eds. *Osteoporosis*. San Diego, Calif: Academic Press. In press.
- Wasnich RD. Consensus and the T-score fallacy. *Clin Rheumatol*. 1997;16:337-339.
- What Factors Are Involved in Building and Maintaining Skeletal Health Throughout Life?**
- Aloia JF, Vaswani A, Yeh JK, et al. Calcium supplementation with and without hormone replacement therapy to prevent postmenopausal bone loss. *Ann Intern Med*. 1994;120:97-103.
- Bassey EJ, Rothwell MC, Littlewood JJ, Pye DW. Pre- and post-menopausal women have different bone mineral density responses to the same high impact exercise. *J Bone Miner Res*. 1998;13:1805-1813.
- Berkelhammer CH, Wood RJ, Sitrin MD. Acetate and hypercalciuria during total parenteral nutrition. *Am J Clin Nutr*. 1988;48:1482-1489.
- Carroll MD, Abraham S, Dresser CM. *Dietary Intake Source Data: United States, 1976-80*. Vital and Health Statistics. Washington, DC: National Center for Health Statistics, Public Health Service; 1983. Publication PHS 83-1681, series 11 (231).
- Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med*. 1992;327:1637-1642.
- Cordain L, Brand-Miller J, Eaton SB, et al. Plant to animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. *Am J Clin Nutr*. In press.
- Cumming RG, Nevitt MC. Calcium for the prevention of osteoporotic fractures in postmenopausal women. *J Bone Miner Res*. 1997;12:1321-1329.
- Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med*. 1997;337:670-676.
- Delmi M, Rapin CH, Bengoa JM, et al. Dietary supplementation in elderly patients with fractured neck of the femur. *Lancet*. 1990;335:1013-1016.
- Devine A, Criddle RA, Dick IM, et al. A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *Am J Clin Nutr*. 1995;62:740-745.
- Fiatarone MA, Marks EC, Ryan ND, et al. High-intensity strength training in nonagenarians. *JAMA*. 1990;263:3029-3034.
- Friedlander AL, Genant HK, Sadowsky S, et al. A two-year program of aerobics and weight training enhances bone mineral density of young women. *J Bone Miner Res*. 1995;10:574-585.
- Haapsalo H, Sievanen H, Kannus P, et al. Dimensions and estimated mechanical characteristics of the humerus after long-term tennis loading. *J Bone Miner Res*. 1996;11:864-872.
- Heaney RP. Effects of caffeine on bone and the calcium economy. *Food Chem Toxicol*. In press.
- Heaney RP. Skeletal health and disease. In: Bogden JD, Klevay LM, eds. *The Clinical Nutrition of the Essential Trace Elements and Minerals*. Totowa, NJ: Humana Press. In press.
- Marcus R. The mechanism of exercise effects on bone. In: Bilezikian JP, Raisz LG, Rodan G, eds. *Principles of Bone Biology*. San Diego, Calif: Academic Press; 1996:1435-1445.
- Nieves JW, Komar L, Cosman F, Lindsay R. Calcium potentiates the effect of estrogen and calcitonin on bone mass. *Am J Clin Nutr*. 1998;67:18-24.
- Robinson TL, Snow-Harter C, Taaffe DR, et al. Gymnasts exhibit higher bone mass than runners despite similar prevalence of amenorrhea. *J Bone Miner Res*. 1995;10:26-35.
- Schürch MA, Rizzoli R, Slosman D, et al. Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. *Ann Intern Med*. 1998;128:801-809.
- Sebastian A, Harris ST, Ottaway JH, et al. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium carbonate. *N Engl J Med*. 1994;330:1776-1781.
- Snow-Harter C, Bouxsein ML, Lewis BT, et al. Effects of resistance and endurance exercise on bone mineral status of young women. *J Bone Miner Res*. 1992;7:761-769.
- Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes: calcium, phosphorus, magnesium, vitamin D, and fluo-

ride. Institute of Medicine. Washington, DC: National Academy Press; 1997.

Taaffe DR, Duret C, Wheeler S, Marcus R. Once-weekly resistance exercise improves muscle strength and neuromuscular performance in older adults. *J Am Geriatr Soc*. 1999;47:1208-1214.

Welten DC, Kemper HC, Post GB, et al. Weight-bearing activity during youth is a more important factor for peak bone mass than calcium intake. *J Bone Miner Res*. 1994;9:1089-1096.

Wyshak G, Frisch RE, Albright TE, et al. Nonalcoholic carbonated beverage consumption and bone fractures among women former college athletes. *J Orthop Res*. 1989;7:91-99.

Zanchetta JR, Plotkin H, Alvarez Filgueira ML. Bone mass in children. *Bone*. 1995;16:393S-399S.

# What Is the Optimal Evaluation and Treatment of Osteoporosis and Fractures?

Agnusdei D, Adami S, Cervetti R, et al. Effects of ipriflavone on bone mass and calcium metabolism in postmenopausal osteoporosis. *Bone Miner*. 1992;19:S43-S48.

Black DM, Cummings SR, Karpf DB, et al, for the Fracture Intervention Trial Research Group. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet*. 1996;348:1535-1541.

Bone HG, McKeever C, Bell N, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. *J Endocrinol Metab*. In press.

Chesnut CH, Silverman S, Andriano K, et al. Prospective, randomized trial of nasal spray calcitonin in postmenopausal women with established osteoporosis: the PROOF study. *Am J Med*. 2000;109:267-276.

Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: re-

sults from the Fracture Intervention Trial. *JAMA*. 1998;280:2077-2082.

Davis JW, Ross PD, Johnson NE, Wasnich RD. Estrogen and calcium supplement use among Japanese-American women. *Bone*. 1995;17:369-373.

Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations and uterine endometrium in postmenopausal women. *N Engl J Med*. 1997;337:1641-1647.

Eddy DM, Johnston CC, Cummings SR, et al. Osteoporosis: review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis. *Osteoporos Int*. 1998;8(suppl 4).

Ettinger B, Black DM, Mitlak BH, et al, for the Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. *JAMA*. 1999;282:637-645.

Garnero P, Hausherr E, Chapuy MC, et al. Markers of bone resorption predict hip fracture in elderly women: the EPIDOS prospective study. *J Bone Miner Res*. 1996;11:1531-1538.

Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med*. 1992;117:1016-1037.

Greenspan SL, Parker RA, Ferguson L, et al. Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women. *J Bone Miner Res*. 1998;13:1431-1438.

Harris ST, Watts NB, Genant HK, et al, for the Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. *JAMA*. 1999;282:1344-1352.

Honkanen RJ, Alhava E, Saarikoski S, et al. Interaction of calcium and HRT in the prevention of bone

loss and fractures in early postmenopausal women. *J Bone Miner Res*. 1999;14:S181.

Komulainen MH, Kroger H, Tuppurainen MT, et al. HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women. *Maturitas*. 1998;31:45-54.

Kovács AB. Efficacy of ipriflavone in the prevention and treatment of postmenopausal osteoporosis. *Agents Actions*. 1994;41:86-87.

Looker AC, Bauer DC, Chesnut CH, et al, for the Ad Hoc Committee on Bone Turnover Markers of the National Osteoporosis Foundation. Clinical use of biochemical markers of bone remodeling. *Osteoporos Int*. In press.

Lufkin EG, Wahner HW, O'Fallon WM, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med*. 1992;117:1-9.

Miller PD, Watts NB, Licata AA, et al. Cyclical etidronate in the treatment of postmenopausal osteoporosis. *Am J Med*. 1997;103:468-476.

Overgaard K, Hansen MA, Jensen SB, Christiansen C. Effect of salcatonin given intranasally on bone mass and fracture rates in established osteoporosis. *BMJ*. 1992;305:556-561.

Overgaard K, Riis BJ, Christiansen C, Hansen MA. Effect of salcatonin given intranasally on early postmenopausal bone loss. *BMJ*. 1989;299:477-479.

Overgaard K, Riis BJ, Christiansen C, et al. Nasal calcitonin for treatment of established osteoporosis. *Clin Endocrinol (Oxf)*. 1989;30:435-442.

Potter SM, Baum JA, Teng H, et al. Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. *Am J Clin Nutr*. 1998;68:1375S-1379S.

Pun KK, Chan LW. Analgesic effect of intranasal calcitonin in the treatment of osteoporotic vertebral fractures. *Clin Ther*. 1989;11:205-209.